POLYMERIC LAMELLAR SUBSTRATE PARTICLES FOR DRUG DELIVERY

Priority is claimed under 35 U.S.C. § 119 to PCT/GB96/01695, filed Jul. 15, 1996, which corresponds to GB 9514285.7, filed Jul. 13, 1995.

The present invention relates to a composition for delivery of an active agent, and more particularly to a composition comprising lamellar polymeric particles.

BACKGROUND OF THE INVENTION

Systems for delivering pharmaceutically or therapeutically active agents, especially antigens, are of considerable interest.

Although the influence of factors such as the dose, formulation and frequency of administration of antigen on the immune response is recognised, optimal delivery and presentation have not in general been established (Khan et al 1994). In conventional liquid dosing regimens, several small doses of antigen are more effective than a single inoculation or a few large doses in stimulating a protective immune response. It is also known that protein concentrations as low as 0.001 μg are sufficient to stimulate a secondary response and that immunological unresponsiveness (tolerance) can be induced by both high and low doses of antigen and by frequent administration.

Many purified, synthetic or inactivated antigens such as Tetanus toxoid are poorly immunogenic and usually require several parenteral doses to confer adequate protection. Adsorption of vaccine antigens onto adjuvants such as Alum is a common method for enhancing the immunogenicity. A wide variety of substances, both biological and synthetic, have been used as adjuvants including mycobacteria, oil emulsions, liposomes, polymer microparticles and mineral gels. A range of 24 different adjuvants was recently investigated by Stieneker et al (1995) for inactivated HIV virus encompassing many of the adjuvant systems currently under investigation. However, only Aluminium hydroxide "Alum" has been approved for administration in humans but its use is often associated with adverse reactions.

As well as protecting antigens, stimulating phagocytosis and activating lymphoid cells, some adjuvants function by retaining the antigen at the site of deposition. Antigen retention appears vital for repeated stimulation of the memory B-cell population and for maintaining antibody titres over long periods (Gray et al 1988). The adjuvant effect of water-in oil emulsions Freund's Complete Adjuvant (FCA)/Freund's Incomplete Adjuvant (FIA), for example, is considered to arise from creation of a short-term 'depot effect' involving antigen retention as a result of granuloma formation. Malarial antigen has been detected at the injection site 80 days post-administration when formulated with liposomes and encapsulated in alginate poly(L-lysine) microparticles (Cohen et al 1991) suggesting that this system also provides a 'depot-type' vaccine for sustained retention and presentation of antigens to the immune system.

The considerable research effort devoted to vaccine formulation has generated a multitude of strategies for optimising antigen release rates and achieving single dose delivery systems. Pulse release of antigen from biodegradable, biocompatible poly(lactide co-glycolide) [PLG] microparticles is considered advantageous for stimulating the conventional, multi-dose, schedule. However, most microparticulate delivery systems are considered to function on the principle of sustained, long term antigen release which presents a continuous trickle of antigen to the immune system to maintain proliferation of immune cells and antibody production. Raghuvanshi et al (1993) developed a single injection formulation for Tetanus toxoid (TT) based on this principle using PLG microparticles. The resultant immune response over 5 months in rats was comparable with the conventional 2-dose schedule of TT adsorbed on alum.

The lower primary response observed with TT adsorbed to Alum was considered due to rapid antigen depletion resulting in reduced proliferation of immune cells.

The ability of small antigen-loaded PLG microparticles (<5 μm in size) to function as potent antigen delivery systems after sub-cutaneous administration is considered to arise from 2 mechanisms: 1) efficient phagocytosis resulting in transport to the lymph nodes where efficient antigen processing and presentation to T-helper cells occurs and 2) controlled release of antigen from the microparticles. (Eldridge et al 1991 O'Hagan et al 1991). However, high immune responses have also been induced using large (72 μm) protein-loaded microparticles (O'Hagan et al 1993) demonstrating that phagocytosis and transport to lymph nodes is not absolutely necessary for achieving high serum antibody titres. However, it is recognised that antigen-containing fragments from large microparticles could be phagocytosed.

It is acknowledged that the higher immune response obtained when using antigen-loaded PLG microparticles could be attributed to an adjuvant effect rather than to slow release of encapsulated protein since antigens adsorbed onto microparticles have been shown to generate potent immune responses after subcutaneous (O'Hagan et al 1993. Kreuter et al 1988) and nasal administration (Alpar and Almeida 1994).

SUMMARY OF THE INVENTION

It has now surprisingly been found that by using biodegradable polymers which are at least partially crystallisable, lamellar substrate particles can be produced which are at least in part crystalline, and which have been found to give improvements in adsorption of antigen, retention of antigen in vitro and improvement in immune response to adsorbed antigens.

The present invention therefore provides a composition for delivery of an active agent comprising a plurality of lamellar particles which particles comprise a biodegradable polymer which is at least in part crystalline, and an active agent adsorbed to at least most of the particles.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is an electron micrograph of prior art spherical particles of poly(DL-lactide-co-glycolide) (PLG).

FIG. **2** is an electron micrograph of L-PLA lamellar particles in accordance with a preferred embodiment of the disclosed composition.

FIGS. **3** and **4** are electron micrographs of the lamellar systems without (FIG. **3**) and with (FIG. **4**) adsorbed influenza virus.

DETAILED DESCRIPTION OF THE INVENTION

The term "biodegradable polymer" includes polymeric systems at least a part of which can degrade into low molecular weight compounds which are known to be involved normally in metabolic pathways. The term also includes polymer systems which can be attacked in the